Docket No.: 20555/1203301-US3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Daniel G. Chain

Application No.: 10/084,380 | Confirmation No.: 3496

Filed: February 28, 2002 | Art Unit: 1649

For: **SPECIFIC ANTIBODIES TO AMYLOID BETA PEPTIDE, PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE THEREOF** | Examiner: G. S. Emch

SECOND DECLARATION OF HOWARD J. FEDEROFF, M.D., PH.D., UNDER 37 C.F.R. §1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Howard J. Federoff declares and states as follows:

1. I am a citizen of the United States, more than twenty-one years of age, and make this Second Declaration in support of this application.

2. I have previously made a Declaration Under 37 C.F.R. §1.132 in support of this application. The contents of my previous Declaration are hereby incorporated herein by reference.

3. I participated in a personal interview held at the Patent and Trademark Office on April 23, 2008 and attended by the Applicant (Dr. Chain), his representatives (myself, Dr. Rock, and patent counsel, Mr. Ludwig and Dr. Bernstein) and the examiners responsible for the application (Examiners Emch, Kemmerer and Stucker). Among the topics discussed at the interview were the Office Action in the application that was on mailed November 19, 2007 ("the

Office Action") and two papers mentioned in the Office Action, Verma et al., *Nature* 369:239-242 (1997) ("Verma") and Phillips, A.J., *J. Pharm. Pharmacol.* 53:1169-1174 (2001) ("Phillips").

4. The Office Action contends that Verma and Phillips provide evidence that gene therapy was and continues to be unpredictable, and therefore casts doubt on my conclusion that provisional application 60/041,850 would have enabled one of ordinary skill in the art to use gene therapy to inhibit accumulation and neurotoxicity of Aβ by contacting soluble Aβ in the CSF of a patient suffering from Alzheimer's disease on April 9, 1997. When the subject arose at the April 23 interview, I told the Examiners that the Verma and Phillips references mentioned in the Office Action did not establish that using gene therapy to practice the invention of the subject application was unpredictable in April 1997.

5. The Examiner's reliance on Verma is based on statements in Verma relating to clinical results of gene therapy and different vectors. Verma's statements concerning clinical results, however, are general in nature and provide no reason to doubt that, as set out in my previous Declaration, on the date it was filed, the provisional application enabled on of ordinary skill in the art to practice gene therapy to inhibit accumulation and neurotoxicity of Aβ by contacting soluble Aβ in the CSF of a patient suffering from Alzheimer's disease.

6. With respect to vectors, Verma includes only a very abbreviated discussion of adeno-associated virus (AAV), the virus I (and the provisional application) identified as a preferred vector for gene therapy in the CNS. According to Verma, AAV particles are laborious to produce, difficult to purify and restricted in DNA payload size. Verma's assertions regarding production and purification of AAV are not well founded. By 1997, multiple laboratories had reproducibly prepared, purified and delivered AAV vector preparations to the brain of mammals. Moreover, by 1997, the payload limitation for AAV had already been established. Thus, by 1997, one of ordinary skill in the art would have readily appreciated that it would have been desirable to express truncated antibody constructs, such as scFv genes, rather than full length antibodies. The provisional application, in fact, sets out a description for the construction of recombinant AAV vectors and for the expression of scFV anti-Aβ in the brain. *See* provisional application at page 39, line 1, et seq. Lastly, Verma raises theoretical questions concerning toxicity and immunogenicity of AAV.

Verma, however, provides no examples or evidence of AAV associated toxicity or immunogenicity; nor am I aware that AAV presents problems related to toxicity or immunogenicity in the context of brain application. Indeed, as set forth in my previous Declaration, Kaplitt et al. (1994, *Nature Genet.* 8:148-154, Exhibit C to my previous Declaration) demonstrated that recombinant AAV could be used to obtain long term expression in the mammalian brain without toxicity and without promoting an immunological response. In short, based on my background and experience in the field of gene therapy since 1988, it is my opinion that any assertions in Verma that may be construed as evidence of the inapplicability of using AAV to practice the claims of the subject application are not well founded.

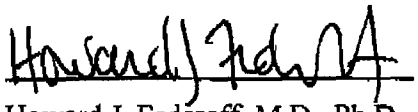
7. The Examiner's reliance on Phillips is based on general statements in the Phillips article relating to clinical results of gene therapy. These statements provide no reason to doubt that, on the date it was filed, the provisional application enabled one of ordinary skill in the art to practice gene therapy to treat Alzheimer's disease. With respect to AAV, Phillips acknowledges that advantages of AAV include efficient transfection of a wide variety of cell types, prolonged expression and low immunogenicity. *See* Phillips at page 1171, Table 2. Phillips cites difficulty in manufacture and limited insert size as supposed disadvantages of AAV. As discussed above in paragraph 6, it is my opinion that these supposed disadvantages are not well founded. Phillips further cites mutagenesis as a potential safety concern related to AAV. *See* Phillips at page 1171, Table 2. In fact, the potential for mutagenesis when using AAV as a vector is low, because recombinant AAV vectors do not integrate into the genome. Thus, it is my opinion that Phillips does not cast any doubt that AAV may be used as a vector to practice the claims of the subject application.

8. In summary, for the reasons set forth in my Declaration submitted to the Patent and Trademark Office on August 29, 2007 and for the further reasons set forth above, it is my opinion that the provisional application provided sufficient information to enable one of ordinary skill in the art to use gene therapy in April 1997 to inhibit accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the CSF of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ, as called for in the claims pending in the subject patent application. No

further information would have been required beyond what is disclosed in the provisional application to practice the claimed invention, nor would it have required undue experimentation.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:



Howard J. Federoff, M.D., Ph.D.

May 19, 2008
Date